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THE ROLE OF STAT3 IN ALZHEIMER'S DISEASE ASSOCIATED AMYLOID BETA DAMAGES

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One of the hallmarks of Alzheimer's disease (AD) is the buildup of amyloid-beta peptide in brain parenchyma and blood vessels. Accumulation of these deposits on blood vessels, known as cerebral amyloid angiopathy (CAA), has been shown to decrease functional reactivity and cerebral blood flow in brain, resulting in cerebrovascular dysfunction and cognitive decline.

Amyloid-beta is also found to cause vascular oxidative stress, suggesting that the toxicity of the protein is related to the production of reactive oxygen species (ROS). Recent studies support this, showing that inhibition of ROS and NADPH oxidase, a transmembrane enzyme that catalyzes production of superoxides, reduces amyloid-beta related deficits in mice. However, the mechanism by which amyloid-beta causes this oxidative stress is not yet well understood.

STAT3 (signal transducer and activator of transcription 3) is known to be a primary regulator of NADPH oxidase and is shown to be activated in higher levels in brains of Alzheimer's patients. We hypothesize that STAT3 is a pivotal upstream regulator of amyloid-beta induced damage.

Our objective for this study was to evaluate the role of STAT3 in behavioral deficits *in vivo*. We used mice bred to express 5 mutations of familial AD, called the 5xFAD model, that are prone to significant amyloid-beta deficits. To inhibit STAT3, 12-month old 5xFAD mice showing CAA were injected with an inhibitor drug, LLL-12, over several weeks. Subsequently, cognitive function was analyzed through novel object location and recognition tests, burrowing behavior tests, and Y-maze tests. We observed improved hippocampal dependent memory in the STAT3 inhibited 5xFAD mice compared to their littermate controls. This suggests that STAT3 plays a key role in amyloid-beta deficits, and could act as an effective therapeutic target for AD patients.